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EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	23

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/301,380	MURPHY ET AL.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *31 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,14,15,18 and 20-33* is/are pending in the application.

4a) Of the above claim(s) *2,14,15,18,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9 and 22-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 April 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: See the PTO-948 mailed with the Office action dated 08/28/02 for the needed corrections of the drawings.

DETAILED ACTION

1. Claims 2, 14-15, 18 and 20-21 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 15.

Claim Rejections - 35 USC § 112

2.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 28 states the composition of claim 23, wherein the tumor cell is a human glioblastoma cell.

Claim 29 states the composition of claim 23, wherein the isolated nucleic acid comprises at least 15 nucleotides corresponding to a portion of SEQ ID NO:1 that is within nucleotides 119 to 2746.

Claim 30 states the composition of claim 23, wherein the isolated nucleic acid comprises at least 15 nucleotides corresponding to a contiguous portion of SEQ ID NO:1 that is within nucleotides 199 to 1434.

Claims 28-30 are indefinite since they lack antecedent basis from claim 23. Claim 23 is a method claim and not a composition claim. It appears that claims 28-30 should be dependent on claim 22 instead.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 3-9, 23-27 and 32-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of administration of the pCMV-1/3Nr-AS to Nr-CAM of SEQ ID NO:1 taught in the specification *in vitro* (cells in cell culture) and via administration to high-grade astrocytomas, gliomas and glio-blastoma tumor tissues for the claimed functions of treatment of said tumors, does not reasonably provide enablement for making and using the breath of claimed antisense molecules to Nr-CAM for treatment of the breath of claimed cells expressing Nr-CAM in a whole organism, including a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 3 is drawn to a method of inhibiting proliferation of a human cell expressing Nr-CAM in a subject comprising administering to the subject an effective amount of a Nr-CAM

antisense nucleic acid comprising at least 15 nucleotides that inhibits Nr-CAM expression, wherein the Nr-CAM antisense nucleic acid is hybridizable in the cell to at least a portion of a RNA transcript of the Nr-CAM gene of SEQ ID NO:1.

Claim 4 states the method according to claim 3 in which the human cell expressing Nr-CAM is involved in a malignancy.

Claim 5 states the method according to claim 4 in which the malignancy is selected from the group consisting of brain cancer, leukemia, and B cell lymphoma.

Claim 6 states the method according to claim 3 in which the subject is a human.

Claim 7 states the method according to claim 5 in which the brain cancer is selected from the group consisting of glioblastoma, glioma, meningioma, astrocytoma, medulloblastoma, neuroectodermal cancer and neuroblastoma.

Claim 8 states the method according to claim 7 in which the glioblastoma is glioblastoma multiforme.

Claim 9 states the method according to claim 3 in which the human cell expressing Nr-CAM is involved with a disease or disorder selected from the group consisting of premalignant conditions, benign tumors, hyperproliferative disorders, and benign dysproliferative disorders.

Claim 23 states the method of claim 3, wherein the Nr-CAM antisense nucleic acid is administered locally.

Claim 24 states the method of claim 23, wherein the local administration is by direct injection.

Claim 25 states the method of claim 4, wherein the Nr-CAM antisense nucleic acid is administered locally by direct injection at the site or former site of a tumor.

Claim 26 states the method of claim 25, wherein the administration is intratumoral.

Claim 27 states the method of claim 3, wherein the human cell expressing Nr-CAM is a tumor cell of the central nervous system and the administration is intraventricular or intrathecal.

Claim 32 is drawn to a method for inhibiting the migratory activity of a tumor cell expressing Nr-CAM in a subject comprising administering to the subject an effective amount of a Nr-CAM antisense nucleic acid comprising at least 15 nucleotides that inhibits Nr-CAM expression, wherein the Nr-CAM antisense nucleic acid is hybridizable in the cell to at least a portion of a RNA transcript of the Nr-CAM gene of SEQ ID NO.:1.

Claim 33 is drawn to a method for inhibiting the ability of a tumor cell expressing Nr-CAM to invade the extracellular matrix in a subject comprising administering to the subject an effective amount of a Nr-CAM antisense nucleic acid comprising at least 15 nucleotides that inhibits Nr-CAM expression, wherein the Nr-CAM antisense nucleic acid is hybridizable in the cell to at least a portion of a RNA transcript of the Nr-CAM gene of SEQ ID NO.:1.

The specification as filed teaches by way of example administration of pCMV1/3Nr-AS and pCMV1/3Nr-AS to mice glioblastomas and reduction of the tumor volume to no tumor. The

specification as filed is enabling for administration of these antisense to glioblastomas by way of injection, but such results do not correlate to the breadth of the claimed invention for treatment of any tumor cell, by any means of administration with any molecule that inhibits Nr-CAM ligand encoding gene function.

In regards to the breath of tumors claimed by inhibition of Nr-CAM, Sehgal et al. (*Int. J. Cancer*: **76**, 451-458, 1998) taught in the abstract that human Nr-CAM is "over-expressed in high-grade astrocytomas, gliomas and glio-blastoma tumor tissues as compared to normal brain tissue. High levels of hNr-CAM expression also were observed in cell lines derived from astrocytomas, gliomas and glioblastoma multiforme tumors. Low levels of hNr-CAM expression were observed in neuroblastoma, meningiomas, melanoma, normal breast and prostate tumor tissues." In view of this teaching, one skilled in the art would not expect that decreasing the expression of Nr-CAM in the tumor cells that normally do not display an elevated expression of the Nr-CAM compared to non-malignant tissues, would have a treatment effect on those tumors. Thus, one skilled in the art would not find that it was predictable to administer the anti-Nr-CAM to the breath of tumors claimed, only those which were known in the art at the time the invention was made to have an increased level of Nr-CAM over wild-type tissue expression levels.

In regards to use of any antisense to Nr-CAM, there is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or

nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetics profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and

chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on

whether these compounds have acceptable properties as drugs. These include pharmacokinetics, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

One of skill in the art would not accept on its face the successful delivery of any Nr-CAM antisense molecule *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art of the unpredictable factors argued above. Specifically the specification does not teach (1) design and stability of any Nr-CAM antisense molecules *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, nor (3) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects of any inhibitory molecule of Nr-CAM administered by any route of administration. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

6. Applicant's arguments filed 1/31/03 have been fully considered but they are not persuasive.

Applicant's response is found on pages 16-23 of the response filed 1/31/03.

Applicant states that "the examples in the specification referred to by the Examiner relate to a standard xenograft murine tumor model system comprising the subcutaneous injection of human glioblastoma cells into mice. Further, the antisense constructs used in the examples were to human Nr-CAM. The claims as amended recite antisense nucleic acids to human Nr-CAM...."

In response, please note the scope of enablement rejection now embraces the breath of claimed organisms (ie. human) since the example in the specification is considered enabling for the administration to human glioblastoma, but only with the antisense construct taught in the specification by way of example. The example in the specification only teaches administration of the pCMV1/3Nr-AS, and does not teach the administration of other antisense which would have a correlated function in treatment of human gliomas for the reasons stated above. Namely, the level of unpredictability is high in the field of antisense therapy and despite the ability to screen individual genes in vitro to find antisense to a particular region, there is no predictable guidance in the art for which such antisense will be able to be used in a whole organism without trial and error *de novo* experimentation as pointed out above. Since the specification must be enabling at the time the invention was made, and at the time the application was filed, one skilled in the art would not have been able to make and use the breath of antisense to the human Nr-CAM gene claimed for uses in a whole organism.

Applicants further note that "[i]nterpretation of the claims must be consistent with the specification in view of the knowledge and skill in the art.... The specification relates, *inter alia*, to inhibition of Nr-CAM function and, with respect to cell proliferation, to inhibition of Nr-CAM

function in cells with high Nr-CAM expression. Thus, the skilled artisan reading the specification would not reasonably interpret the claims to read on antisense for inhibition in "any tumor cell." Moreover, claim 1 recites "...in an amount effective to inhibit hyperproliferation of a tumor cell having high *Nr-CAM* expression".

In response, claim 1 is no longer rejection under 35 U.S.C. 112, scope of enablement, and claim 3 (the broadest independent claim), claims inhibition of any human cell in a whole organism expressing Nr-CAM. Thus, the rejection is now drawn to the breath of human cells expressing Nr-CAM in any whole organism as claimed. A new reference, Sehgal et al., teaches that Nr-CAM is not overexpressed in every type of malignant cell, and thus one skilled in the art would not predictably inhibit any cell type from expression of antisense to Nr-CAM based on this finding.

Applicants further state that "in addition to unpredictability of the art, various other factors must be considered, including *inter alia*, the amount of experimentation necessary, the state of the prior art, the relative skill of those in the art, and the nature of the invention, among others.... Thus, predictability must be viewed in relation to balancing all of the factors."

The above rejection considers these factors based on the literature cited. It was known in the art at the time the invention was made (and remains in the art) that there is a high level of unpredictability as to which antisense to a target gene may function in a whole organism. The physiology of a whole organism is not the same as that of a cell in cell culture. There are numerous factors to be considered *in vivo* that do not arise *in vitro*. The nature of the instant

invention is treatment of a human with a breath of antisense compounds. As shown in the Branch reference, part of the difficulty in use of antisense as a pharmaceutical compound *in vivo* lies in the ability to provide a suffient concentration of the antisense to the localized target cell/tissue, such that sufficient amount of gene inhibition may be achieved absent toxic levels of compound (which of course would counteract any therapeutic advantage of using the antisense). Thus, since antisense function by binding to the target nucleic acid, and strength of hybridization varies significantly based on the sequence of that antisense/target sequence, the composition of the cellular environment, and accessibility of the target site, the ability of antisense to function in a whole organism must be considered on an antisense-by-antisense basis. Since there was no disclosure of guidance to one of skill in the art at the time the invention was made to make the antisense for use *in vivo* (and in fact while certain antisense fragments were taught in the specification as filed, none of them were administered to cells). Any of the patents issued to ISIS Pharmaceuticals Inc. for antisense to a particular gene target demonstrates the variability of results in design of antisense to a gene region. Their tables show the percent inhibition of a target gene in cell culture, and that different antisense have different capacities to inhibit the target gene. There is currently no known correlation between antisense to one gene and antisense to another gene regarding ability to inhibit. Each antisense must be tested. Since the examples in the prior art of antisense to other genes do not correlate to specific design of antisense to Nr-CAM, one skilled in the art would necessarily practice *de novo* trial and error experimentation to find an Nr-CAM antisense that has the claimed functions other than the specific antisense

disclosed in the specification as filed. Because of the high level of unpredictability in the art for making an antisense for *in vivo* use, the amount of *de novo* experimentation required, absent further guidance, is considered undue.

Applicants state that Ma et al. taught that antisense "design is based on one unifying concept of base pairing between complementary nucleic acid sequences...." This point is not disputed. However, the other factors considered unpredictable were listed above in regards to making and using antisense based on design to a target nucleic acid sequence. There are still numerous obstacles to overcome even with knowing the target nucleic acid sequence.

Applicants further state that "[h]ere the state of the art is such that the various characteristics recited can be addressed by particular design criteria known to the skilled artisan and those design characteristics described in the specification as filed. In fact, it appears that the statement cited by the Examiner may be merely a list of characteristics that an antisense molecule must have to be clinically effective as the remainder of the section in Ma *et al.* goes on the discuss how the art has approached and overcome each of the potential issues to achieve the characteristics listed." (The characteristics referred to are resistance to degradation, ability to internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable phamaceokinetic profile and be nontoxic)

While the last two recited characteristics deal more with pharmaceutical use of the antisense *in vivo*, the degradation issues, internalization issue and accessibility issue are all facts that are problematic *in vitro* as well as *in vivo*, and do not correlate from *in vitro* use to *in vivo*

use (Branch and Flanagan). Thus, these issues are not merely clinical issues as discussed by applicant, but are obstacles that must be overcome to make and use the claimed invention.

Applicants further state that "Applicants have demonstrated I) that Nr-CAM is involved in tumorigenesis of certain cancers, ii) that the inhibition of over expression of Nr-CAM can reduce the proliferation and migration of certain tumor cells, and iii) that antisense molecules can be used to reduce the expression of Nr-CAM *in vitro* and *in vivo*. Applicants have provided two specific examples of methods for introducing anti-sense molecules into cells. These methods include introduction of antisense by recombinant retroviral transformation and injection of antisense hNr-CAM expressing plasmids mixed with lipsomes into mice. Applicants also provide three anti-sense molecules 17 to 21 nucleotides in length that will hybridize with the 5' end the Nr-CAM gene designed in view of the characteristics discussed above that are expected to hybridize with mRNA encoding Nr-CAM and to reduce the expression of Nr-CAM."

However, as pointed out above, the teachings of the specification as filed do not provide sufficient guidance to enable the breath of antisense claimed nor the breath of tumor cells claimed since the majority of what applicant relays above was only prophetically taught in the specification as filed and was not taught by exemplification.

Applicants further refer to several documents to teach "that, at the time of filing of the instant application, various methods were known in the art that address the issues of cellular uptake and stability of oligonucleotides *in vivo*, resulting in increased resistance to degradation as well as increased penetration into cells." However, isolated examples taught in the art for

making and using antisense *in vivo* do not correlate to use of any possible antisense *in vivo* absent trial and error experimentation as stated above. Because of the unpredictable factors argued above, one of skill in the art must individually test each antisense candidate for *de novo* determination of the ability to have the claimed functions. This testing is more than routine because there is no guarantee or assurance that even if you test all possible combinations of antisense of a specific size to a known target gene, that you will be able to find one that has the desired functions *in vivo*.

Applicant further argues that Green et al. and Bennett et al. both teach that a delivery reagent is not required for administration of antisense *in vivo*. Please note that this aspect of the rejection has been withdrawn. However, the unpredictability in the art remains for the ability to deliver the antisense to the desired location of any cell, or any tumor cell instantly claimed for the claimed functions of reduction of Nr-CAM based on the unpredictability in the art recited above for making specific antisense having *in vivo* uses.

Applicant further argues that Ma et al. provides documentation that in regards to antisense to dopamine receptor, that antisense may be "readily designed" to "differentially inhibit a specific receptor *in vivo*, unlike conventional antagonists which interact with multiple subtypes." However, while most of the references cited are optimistic about the potential of antisense technology in general, they simulatanously teach all the unpredictable factors stated above. The relative usefulness of antisense in comparison with other types of drug candidates does not serve to establish guidance to one skilled in the art for making and using antisense to a

particular target gene for a particular *in vivo* function. The standard argued above in the rejection is not one of the relative use of antisense to other types of potential pharmaceuticals for inhibition of Nr-CAM, but rather based on the documentation shown above that antisense to date has numerous obstacles, despite the optimism in the field.

Applicant further notes that "the skilled artisan would recognize that antisense candidates for intracellular hybridization can be evaluated before screening on cells by known methods for determining complementary nucleic acid sequences that will exhibit specific hybridization coupled with consideration of cellular temperature and ionic content, which can be mimicked by manipulation of *in vitro* hybridization temperature and ionic conditions. Also, Branch does not state that empirical methods cannot reliably determine effective antisense molecules from a given set of candidates. Empirical methods do not by themselves constitute undue experimentation, nor do these methods speak to the predictability of success."

It is not contested that one of skill in the art would have readily had the tools to screen for an antisense that has some function in cells in cell culture to inhibit the target gene. However, this ability does not further provide guidance to one skilled in the art pertaining to use of any such antisense *in vivo*. The Branch reference was supported by the other cited references in teaching that there were many more factors to consider *in vivo* than *in vitro*.

Applicant further states in regards to the unpredictable factors taught by Jen et al. that "such considerations can be addressed by the skilled artisan and, thus, the level of predictability relating to in vivo specificity does not render the claims nonenabled...." However, the state of

the art remained at the time the invention was made, unpredictable, since the guidance that was needed to practice the claimed invention was specific, and not general guidance argued by application as the ability of one skilled in the art to "address" the unpredictable considerations.

The remaining arguments refer to previous points not repeated in the above rejection.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claima 1, 22 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Lane et al. (*Genomics*, Vol. 35, pp.456-465, 1996).

Claim 1 is drawn to a composition for the inhibition of tumorigenesis comprising a pharmaceutical carrier and an antisense nucleic acid comprising at least 15 nucleotides hybridizable in a cell to at least a portion of an RNA transcript of a Nr-CAM gene of SEQ ID NO:1 in an amount effective to inhibit tumorigenesis by inhibiting hyperproliferation of a human tumor cell having high Nr-CAM expression. Claim 22 states the composition of claim 1, wherein the composition is formulated as a liquid.

Claim 31 is drawn to an isolated nucleic acid comprising at least 15 nucleotides, the isolated nucleic acid hybridizable, under highly stringent conditions comprising hybridization in an aqueous solution containing 6X SSC at 65 C, to at least a portion of a messenger RNA having SEQ ID NO:1 and encoding human Nr-CAM, wherein the oligonucleotide inhibits the expression of Nr-CAM in a tumor cell.

Lane et al. teaches on page 457, col. 2, lines 25-26, the sequence of an antisense oligonucleotide to human Nr-CAM, which absent evidence to the contrary would have the inherent function of binding the human Nr-CAM transcript in a tumor cell in cell culture. The hMr-CAM gene referred to by Lane et al. is the same sequence as referred to in the instant specification as filed on page 103, line 2. Thus, the antisense primer taught by Lane et al. has 100% homology to instant SEQ ID NO:1, human Nr-CAM. Thus, the primer/probe taught by Lane et al., having met all the structural requirements instantly claimed, would inherently meet the functional requirements claimed due to the inhibition of the hNr-CAM gene (instant SEQ ID NO:1) via antisense mechanisms. Furthermore, the instant specification on page 87, states the the carrier and liquid in the pharmaceutical comprise water or a buffer. The PCR buffer taught by Lane et al. would thus meet the instant limitation of a carrier or liquid in conjunction with the antisense.

9. Claims 3-9, 21, 23-30 and 32-33 are considered free of the prior art since the prior art taught as in Sehgal et al. the over-expression of hNr-CAM in certain tumors but did not teach

methods of use of antisense to h-Nr-CAM for the function of inhibition of tumorigenesis in a tumor cell, nor motivation nor an expectation of success to inhibit hNr-CAM expression in tumor cells.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
May 5, 2003

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600